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DEPARTMENT OF GENETICS
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Dr. Sidney Brenner
MRC Unit for Molecular Biology
Cambridge University
England

Dear Sidney:

Thanks for sending the mimeographed manuscript of your intriguing idea on mutagenesis.

There is one combination of circumstances that this proposal suggests - I wonder if it has been looked for. This will not apply to a comma-less code or to one where there are artificial phase markers ("synch lines") at frequent intervals. But suppose we still consider the old idea of a sequence without singularity which must be read in proper triplets from beginning to end. I don't know if you have given this a name; perhaps we might call this a phase-shift-sensitive code. On this model, mutants that have been induced with acridine should also lead to a profusion of quasi-reversions under the influence of the same agent. Some of these would have the wild type amino acid sequence; others, as you suggested, might have substitutions for one or more adjacent amino acids. This would be by virtue of the misreading from phase disturbance between a deletion and an insertion. One would guess that mutant protein modified in this way should frequently have requisite activity but fall short of that displayed by the wild type. So on this rather stringent model, one might then guess that you would see a profusion of near reversions. I don't know if this would be better calculated to test the coding ~~protein~~ hypothesis - which is perhaps not a very appealing one in any case - or your suggestion of the mechanism of action of acridine. But if you can continue to substantiate the latter with further experiments, it then might be quite useful in deciding about the code.

Yours sincerely,

Joshua Lederberg
Professor of Genetics